Application and Use of Dose Estimating Exposure Model (DEEM) for Dose Comparisons After Exposure to Trichloroethylene (TCE)

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1 Abstract

DEEM, developed over the last few years, is a model architecture for estimating internal tissue doses resulting from actual or simulated exposures. Exposure profiles are inputted into DEEM through scenario-based modules or through time-histories of exposure concentration. The relationship of exposure to dose is complex and depends on many factors and is different for each choice of dose.

In this example DEEM was specifically configured to simulate TCE pharmacokinetics in the human. The model was first tested against data taken from human volunteers (Fisher, et al.). Next we looked at the impact of different exposure regimens on various internal measures of dose for TCE. Our "base" exposure was 30 ppm for eight hours repeated for five days. The results of this exposure were compared to several profiles whose time-weighted average was 30 ppm over the 8-hour period. The profile concentrations ranged anywhere from 0 to 131 ppm to give the time-weighted 30 ppm average. The peak height of TCE concentration in the blood varied considerably upon exposure concentration, duration, and frequency as well as physiologic factors. In contrast, concentrations of the metabolites of TCE, trichloroacetic acid (TCA) and trichloroethanol (TCOH), were virtually the same regardless of which exposure profile was simulated. In some circumstances, for these measures of internal doses, an 8-hour average exposure suffices for their estimation. We present several different simulations to examine the impact of exposure on internal dose. Findings such as these could have impact on future exposure study designs.

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2 Background

DEEM is a physiologically based pharmacokinetic (PBPK) computer model which mathematically describes and predicts toxicologically relevant doses within the body (e.g. concentration of exposure chemical within tissues, concentration of the chemical's metabolites within body, etc.). The development goal of DEEM is to provide toxicologists, exposure assessors, and risk assessors with an easy to use standard framework for calculating and predicting dose within the body. Exposure profiles are inputted into DEEM through scenario-based modules or through time-histories. Time-histories are a description of the sequence of exposures to a chemical that an individual receives describing the concentration of the exposure as a function of time. For the simulations given in this presentation, DEEM was specifically configured to simulate trichloroethylene (TCE) pharmacokinetics in the human. TCE is metabolized in the liver to trichloroacetic acid (TCA) and trichloroethanol (TCOH). TCOH is intern metabolized to TCOG (glucuronidated TCOH) and dichloroacetic acid (DCA). TCA, DCA, and TCOG are eliminated from the body in urine. There were 37 parameters that were obtained from Fisher et al. and the literature on TCE metabolism that were inputted into DEEM to create the simulations presented here. The model was then tested against data taken from human volunteers (Fisher, et al.) and found to provide excellent correlation between experimentally derived data and model simulations.

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3 The Question

Concern has been raised on whether using the average of chemical concentrations in air over a specific time period in calculating exposure is as reliable and as accurate compared to using multiple or continuous measurements in estimating exposure. Using DEEM, exposure to dose experimental simulations were designed that would answer this question.

4 Experimental Design

Three different exposure regimens (representing the same individual in a different environment) were developed to approximate a five day, eight hour a day work place containing varying exposure levels of TCE such that the random distribution of inhalation concentration of TCE for each work day was 30 ppm. The simulated individual was a non-gender specific 70 kg person whose bio-physiological parameters are listed in the first table. The length of time for each simulation was 168 hours approximating a time history of a 5 day work week with a two day nonwork (no exposure) weekend. The three different time histories were identical for each day of their respective work week. The second table shows the time history for one of these random distribution exposure regimens. A fourth exposure regimen for the same individual with a work environment with a fixed inhalation concentration of 30 ppm was also created. The four simulated TCE exposure scenarios, three varying and one fixed, were run on DEEM and separate plots were created for 1) TCE, TCOH, and TCA concentrations in venous blood over time, 2) TCE, TCOH, and TCA Area Under the Curve in venous blood over time, and 3) amounts of TCA and TCOG in urine over time. Because of little interest of exposure assessors in DCA, no plots of DCA were run.

5 Results

As would be expected the plots of the three variable air levels of TCE differed among themselves and from the fixed air level producing blood concentrations varying by more than a factor of 5. The surprising results were obtained when the concentrations of the metabolites of TCE were compared. The concentrations of venous blood TCOH and TCA, the Area Under the Curve (AUC) for TCE, TCOH and TCA, and the urine amounts of TCA and TCOG were identical for all three variable concentrations of TCE and the fixed air concentration of TCE. Except for TCE concentrations in blood, the plots of the TCE and its metabolites for the **varying** 30 ppm TCE in air simulation one (given in the table) and the plots for the **fixed** 30 ppm TCE in air simulation shown in the poster are virtually indistinguishable from each other.

6 Bio-Physiological Parameters for Simulated Person in DEEM

MODEL PARAMETER	MEAN
PARTITION COEFFICIENT	
TCE-FAT	52.34
TCE-Kidney	1.08
TCE-Liver	4.85
TCE-Lung-Blood	0.39
TCE-Lung-Air	11.15
TCOH-Liver	0.59
TCA-Liver	0.66
TCA-Kidney	0.66
TCOG-Liver	0.6
TCOG-Kidney	1.4
DCA-Liver	0.8
DCA-Kidney	0.8

SATURABLE METABOLISM	Mg/Hour
TCE-TCA-Km	10.8
TCE-TCA-Vmax	6
TCOH-TCOG-Km	160
TCOH-TCOG-Vmax	30
TCOH-DCA-Km	10
TCOH-DCA-Vmax	0.1

MODEL PARAMETER	MEAN
VOLUME	**LITERS**
Body Volume	70
Muscle for Lower Limit	59.462
Muscle for Upper Limit	27.338
Given Fat	14
Kidney	2.8
Liver	1.82
Lung	0.98
Venous Blood	2.1

BLOOD FLOW	LITER/Hour
Alveolar Ventilation	450.12
Given Cardiac Output	384.78
Fat	18.46944
Kidney	75.80166
Liver	92.3472

LINEAR METABOLISM	1/Hour
TCOH-TCA-Rate-Const	7

LINEAR ELIMINATION RATE CONST.	1/Hour
TCA-Urine	0.75
TCA-Liver	0.2
TCOG-Urine	40
DCA-Urine	0.00795
DCA-Liver	7.0873

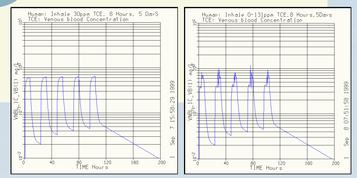
7 Time History for Random Distributions of TCE

For eight hour work days 1-5

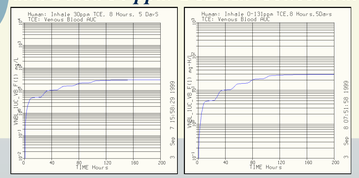
Simulation One

Time: Hours	Concentration: ppm
0	35
0.5	25
2	18.5
4	131
4.25	25
5	0
5.5	75
6	25
7.5	35
8	0

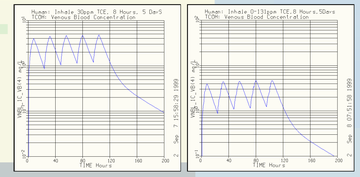
8 Plots of Concentration of TCE in Venous Blood Over Time For: Variable Time Weighted Average 30 ppm TCE, and Fixed 30 ppm TCE Air Concentrations



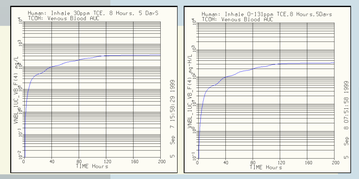
9 Plots of the Area Under the Curve of TCE in Venous Blood Over Time For: Variable Time Weighted Average 30 ppm TCE, and Fixed 30 ppm TCE Air Concentrations



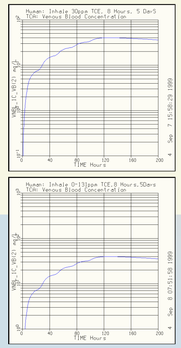
10 Plots of Concentration of TCOH in Venous Blood Over Time For: Variable Time Weighted Average 30 ppm TCE, and Fixed 30 ppm TCE Air Concentrations



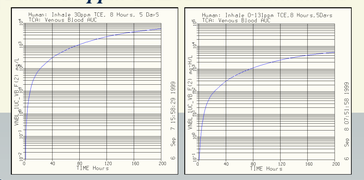
11 Plots of the Area Under the Curve of TCOH in Venous Blood Over Time For: Variable Time Weighted Average 30 ppm TCE, and Fixed 30 ppm TCE Air Concentrations



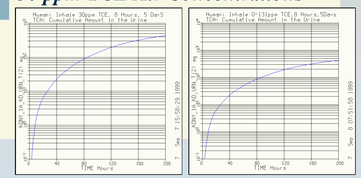
12 Plots of Concentration of TCA in Venous Blood Over Time For: Variable Time Weighted Average 30 ppm TCE, and Fixed 30 ppm TCE Air Concentrations



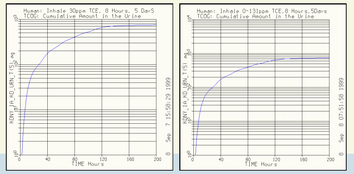
13 Plots of the Area Under the Curve of TCA in Venous Blood Over Time For: Variable Time Weighted Average 30 ppm TCE, and Fixed 30 ppm TCE Air Concentrations



14 Plots of Urine Amounts of TCA Over Time For: Variable Time Weighted Average 30 ppm TCE, and Fixed 30 ppm TCE Air Concentrations



15 Plots of Urine Amounts of TCOG Over Time For: Variable Time Weighted Average 30 ppm TCE, and Fixed 30 ppm TCE Air Concentrations



16 Conclusions

For exposure assessment and depending on the dosimetric, the use of an average of concentration of exposure over a given time period may be as reliable and more cost effective than the collection and use of many data points. The validity of these conclusions will be further tested against simulations and experimental data for other chemicals and over a range of different individuals and body types found in the general population.